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## Angiotensin converting enzyme inhibition in chronic renal failure and hypertension

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## Summary

### *Chapter 1*

In patients with a history of renal disease the kidney shows a gradual, in most cases linear, loss of function even when the underlying kidney disease has been cured. However, the rate of renal function decline shows a large interindividual variation. The independency of this process suggests that not the renal disease itself but other factors are responsible. In the past decades, many of those factors have been identified. One of the most important of these modifying factors is a change in renal hemodynamics leading to a rise in intraglomerular pressure. In situations where a large number of nephrons are removed or malfunctioning due to underlying disease, the kidney tries to maintain filtration by increasing the pressure in the remaining healthy nephrons through afferent vasodilatation, efferent vasoconstriction or both. The renin-angiotensin system, which is often activated in renal disease, plays an important role in inducing these renal hemodynamic changes. However, this short-term beneficial compensatory hemodynamic mechanism appears to be deleterious in the long-term: the increased intraglomerular pressure induces focal and segmental glomerulosclerosis, which may eventually lead to end-stage renal failure. In recent years, many measures aiming at prevention or amelioration of renal function decline have been studied. Counteracting the renin-angiotensin system with angiotensin-converting-enzyme inhibitors (ACE inhibitors) is among the most promising of these measures. These drugs have been shown to be beneficial in many animal models. However, in humans their effectivity is less convincing and prospective trials are ongoing. One of these trials was started in Groningen, in 1988, comparing the ACE inhibitor enalapril and the  $\beta$ -blocker atenolol with respect to their effect on long-term renal function decline.

### *Chapter 2.*

This chapter gives an overview of the management of chronic renal failure. Apart from intraglomerular pressure elevation several other possible causes of progressive renal function loss are mentioned. Animal data on progressive renal function loss may to a certain extent be extrapolated to the clinical setting.

Next, various interventions aiming at halting the progression of renal function loss are discussed. Immunosuppressive therapy has been used in renal diseases with immunologic mechanisms of disease progression. In other renal diseases, their value is

## *Chapter 9*

still debated. Even if immunosuppression is shown to slow renal function decline, a comparison with alternative therapies is necessary because of the relative dangers of the former. Antihypertensive therapy has been shown to be beneficial in several studies in patients with renal disease, especially in diabetes. Dietary protein-restriction has been found to retard renal function decline in the first prospective studies, although a recent large multicenter study (Modification of Diet in Renal Disease, MDRD) found no significant protective effect in patients with renal insufficiency. ACE inhibitors possess an additive renal protective effect over conventional antihypertensive therapy, as shown in several recent studies. However, most of these studies were small, retrospective or non-randomized. Larger multicenter trials are ongoing. Proteinuria by itself may play a direct role in causing progressive renal function deterioration. Thus, the antiproteinuric effect of different therapeutic regimens may be renoprotective only by reducing the protein load of the nephrons. However, since it is hard to dissociate the antiproteinuric effect of these regimens from their concomitant effects on glomerular hemodynamics, it remains unproven whether the direct reduction in nephron protein load is responsible for the renal protective effect. Clinical evidence that an antiproteinuric effect prevents renal function loss is limited. Evidence is growing that lipid-lowering agents might be renoprotective.

## *Chapter 3.*

In this study the antihypertensive and renal effects of the ACE inhibitor lisinopril were studied in a group of patients with impaired renal function and hypertension. After twelve weeks of treatment most of the patients showed a good blood pressure response to lisinopril. During this period, both glomerular filtration rate (GFR) and filtration fraction (FF) fell by approximately 20 % whereas effective renal plasma flow (ERPF) remained stable. During a one-year follow-up period, the lisinopril dose could be lowered gradually in a subset of patients with a stable diastolic blood pressure, without losing the antihypertensive effect. With respect to renal hemodynamics, GFR decreased in two thirds of the patients, whereas GFR remained fairly stable in the other third. In this latter group the pre-treatment GFR was higher and the effective renal plasma flow had increased. In contrast, in the group with a decline in GFR, pretreatment GFR was lower, and lisinopril had induced a decrease in ERPF without any change in FF. Thus, the ACE inhibitor lisinopril is an effective antihypertensive drug in patients with renal function impairment. Interestingly, lisinopril increases ERPF and stabilizes GFR in the

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subgroup of patients with a higher pre-treatment GFR, which could suggest that therapy should be started early to reach an optimal renoprotective effect.

### Chapter 4

In this chapter the question is addressed whether there are quantitative differences between different ACE inhibitors with respect to their influence on renal versus systemic hemodynamics. Such a difference could guide the choice for a specific ACE inhibitor in certain disease conditions. A single-blind cross-over study was performed in 8 patients with essential hypertension and normal renal function, comparing the ACE inhibitors enalapril and lisinopril. Interestingly, with the same blood pressure reduction, ERPF rose more on enalapril than on lisinopril. Likewise, filtration fraction (FF) and renal vascular resistance (RVR) decreased more on enalapril than on lisinopril. Counteracting these ACE-inhibitor-induced changes by angiotensin II infusion resulted in a more marked response of ERPF, FF and RVR during enalapril as compared to lisinopril. We concluded that in a situation of a comparable systemic blood pressure reduction, enalapril has a greater effect on renal hemodynamics than lisinopril. Enalapril could thus be a more effective renoprotective antihypertensive drug.

### Chapter 5

In chapter 5 the question is addressed whether the antiproteinuric effect of an ACE inhibitor is solely due to its blood pressure lowering effect or to its specific effects on the kidney. Therefore, the antihypertensive, renal hemodynamic and antiproteinuric effects of the ACE inhibitor enalapril and the  $\beta$ -blocker atenolol were compared in a prospective, randomised, double blind study in 27 patients with proteinuria of non-diabetic origin, hypertension and moderately impaired renal function. The fall in systolic and diastolic blood pressure was not different between both groups. However, although mean proteinuria fell slightly during atenolol, the fall that was observed during enalapril treatment was significantly greater. In both groups filtration fraction fell, the fall being greater on enalapril than on atenolol. We concluded that enalapril lowers proteinuria more than atenolol in patients with non-diabetic renal disease, despite a similar blood pressure lowering effect of both drugs. This antiproteinuric effect of angiotensin converting enzyme inhibitors appears to be associated with the characteristic renal haemodynamic effect of these drugs.

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### Chapter 6

Reliable measurement of renal function is of paramount importance in long-term intervention studies on the progression of chronic renal failure. Sequential accurate determination of glomerular filtration rate (GFR) measuring the renal clearances of exogenous tracers such as iothalamate is the most accepted method in this respect. However, due to inaccuracies in urine collection without bladder catheterisation, intratest variation, and thus intertest variation, of this gold standard UV/P method is considerable. This impacts on the accuracy of long-term slope estimations. A previously described method of GFR determination based on simultaneous infusion of  $^{131}\text{I}$ -hippuran and  $^{125}\text{I}$ -iothalamate has been shown to correct for inaccurate urine collection. To investigate whether this combined infusion method indeed improves the accuracy of GFR measurements and thus improves GFR slope accuracy in intervention trials, we analyzed longitudinal GFR data obtained in 71 patients with renal disease, during a follow-up of 84 to 180 weeks. The correction method yielded an almost five times smaller intra-test coefficient of variation (CV) and a twice smaller inter-test CV than the standard method. These smaller CV's in GFR measurements using the correction method had a clear impact on slope accuracy. All error parameters of the regression equation were significantly smaller using corrected GFR. Also, the range of slopes was almost twice as low using the correction method. Interestingly, the improvement reduced the necessary sample size needed to detect a certain difference between different interventions to about 30% of the necessary sample size when using the standard method. We conclude that the accuracy of GFR measurements is improved using the hippuran correction method. The resulting improvement greatly enhances the accuracy of long-term GFR-slope calculations. A possible difference between two treatment modalities may thus be detected more rapidly using this corrected GFR measurement method.

### Chapter 7

Not all patients with impaired renal function respond equally well to therapy aiming at prevention of further renal function deterioration. Therefore, markers predictive for a good response to therapy, which can be evaluated at the start of treatment or directly thereafter could be of value. One of those markers could be the initial antiproteinuric effect of a certain intervention. Thus, we evaluated whether the short-term antiproteinuric response induced by antihypertensive treatment in non-diabetic proteinuric patients is

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predictive for a long-term beneficial effect on renal function decline. Twenty-nine patients with proteinuria and impaired renal function were treated with enalapril or atenolol. After 12 weeks treatment FF and proteinuria had fallen significantly. A great interindividual difference in antiproteinuric response was noticed. During long-term follow up a fall in mean GFR was observed with considerable interindividual variation. The slope of this GFR decline correlated with the short term responses of proteinuria and filtration fraction, but not with the blood pressure response. We conclude that the magnitude of the initial reduction in proteinuria and filtration fraction induced by either enalapril or atenolol predicts the effect of that treatment on long-term GFR decline. This observation may be important in identifying responders to continued treatment in an early phase as far as renal function protection is concerned.

## Chapter 8

In this chapter we focus on a possible other predictive marker for treatment response in long-term intervention studies: the initial decline in GFR which may occur after starting therapy. Such an initial change in GFR is suggested to be the result of a treatment-induced intraglomerular pressure fall. If so, it should be reversible after treatment withdrawal. Moreover, the magnitude of such a hemodynamic change could predict whether long term renal protection will occur during continued treatment. We therefore investigated 40 hypertensive non-diabetic patients with impaired renal function, who were enrolled in a double blind intervention trial. After a placebo baseline period they were randomly assigned to treatment with either atenolol or enalapril. Study parameters were measured at baseline, after 12 weeks (treatment titration), each subsequent 24 weeks during follow-up, and 12 weeks after treatment withdrawal. Mean GFR fell rather steep during the first 12 weeks and showed a less steep decline during follow-up. The initial acute treatment induced decline in GFR correlated with the long-term GFR slope: the more initial GFR fall, the better the long-term slope. After 4 years of treatment, withdrawal for 12 weeks resulted in a significant rise in GFR. The initial fall in GFR was related to the rise after withdrawal. The patients were divided in a group A that showed an initial fall in GFR and a group B in whom GFR initially did not change. Group A had a significantly less steep slope than group B. In group A GFR increased again after withdrawal of treatment, whereas it did not in group B. As a consequence, GFR post-treatment was not different compared to pre-treatment in group A, whereas it was significantly lower in group B. In conclusion, an initial fall in GFR is reversible

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even after years of treatment, suggesting that this therapy-induced fall is of hemodynamic and not structural origin. This initial GFR fall appears to predict the subsequent degree of renal protection during long-term follow-up.

### *Future perspectives*

The future use of ACE inhibitors as renal protective agents will depend on the results of large clinical trials proving their efficacy. At this moment substantial clinical proof is available for the antiproteinuric effects of these agents, however, their alleged renal protective effect is, in contrast to animal data, far less convincing. With more inconclusive data from larger intervention studies becoming available, the question even rises whether it will ever be proven unequivocally that ACE inhibitors indeed possess a renal protective effect. Why is the efficacy of these drugs so difficult to proof?

First, dilution by non-responders may play an important role. It has become clear from several studies that, although a large group of patients may benefit from renal protective treatment, responses vary considerably between different individuals. A relatively small group of non-responders or non-compliers on a certain treatment may influence the mean value of an outcome measure heavily, thereby hiding a potential beneficial effect of such a treatment. Secondly, inaccuracies in GFR measurements (see Chapter 6) may leave a true difference between two interventions undetected. With respect to the former it thus seems of extreme importance to identify the patients who would probably benefit the most from a certain treatment before the actual intervention is started. These patients may be identified by markers predictive for the magnitude of future renal function decline. Two of these potential markers, i.e. proteinuria and initial GFR response, have been discussed in the preceding two chapters. Several other potential predictive markers are currently evaluated. For instance, plasma homocysteine levels increase with progressive renal function deterioration [1]. This could be an epiphenomenon, but the homocysteine level may also be a predictive marker since it might reflect the level of endothelial dysfunction [2]. The plasma lipoprotein(a) [Lp(a)] level is an independent risk factor for atherosclerosis. In hemodialysis patients the incidence of atherosclerotic events appears to be higher in hemodialysis patients with increased plasma Lp(a) levels [3]. It is imaginable that a high Lp(a) level in chronic renal failure might be associated with a steeper decline in renal function. Interestingly, higher Lp(a) levels are also present in hypertensive patients with salt-sensitivity, which is another riskfactor with respect to renal function decline. Thus, several predictive markers seem to coincide, which supports

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the hypothesis that progressive renal function decline is a multifactorial process. Pharmacologic intervention aiming at diminishing serum levels of these potential markers might be a promising approach in the further prevention of renal function decline. Future studies should address these issues. Another unresolved issue concerns the optimum moment of intervention. Is it preferable to start treatment with an ACE inhibitor early in the course of the disease at the time the patient has minimal loss of GFR and treatment responses could still be optimal? Extrapolating animal data, this seems the most promising approach. However, compliance in these patients without any complaints will probably be worse than in patients with more advanced renal disease. Moreover, in many patients the first contact with a clinician takes place when renal function deterioration is already substantial. Remarkably however, a recent intervention study by Kamper et al showed a positive treatment result in patients with a low GFR [4].

Genetics may also be important in renal function decline. In the gene coding for angiotensin converting enzyme an insertion-deletion polymorphism occurs giving rise to 3 different ACE-genotypes, the II, ID, and the DD ACE-genotype. Phenotypically, patients with the II-genotype show low serum ACE-levels, whereas the patients with DD-genotype have the highest serum-ACE levels [5]. The presence of the DD-genotype has been shown to be an independent riskfactor for myocardial infarction [6]. It is imaginable that this DD-ACE-genotype may also turn out to be a riskfactor for renal function decline. Even more intriguing is the question whether a potential beneficial effect of treatment with an ACE-inhibitor is dependent upon the presence of one of these genotypes. As a final remark, although several advantages of treatment with ACE-inhibition have been highlighted in this thesis, it must be kept in mind that ACE plays an important role in various organ systems. Our present approach of unselective ACE inhibition might have disadvantages in the long run. In this respect it is intriguing that the ACE DD-genotype, the type with the highest serum ACE levels, is surprisingly more frequent in centenarians than in younger people [7]. Leaving open the questions whether the opposite is also true or whether it is desirable to become a centenarian, this observation strikes a note of caution with respect to a drastic suppression of serum (high) ACE levels.